```
=> d his

     (FILE 'HOME' ENTERED AT 15:49:22 ON 13 FEB 2003)

     FILE 'CAPLUS' ENTERED AT 15:49:39 ON 13 FEB 2003
L1          638 S CELL(P)HYPOXI?(P)(RE(W)OXYGENAT? OR REOXYGENAT?)
L2         1089 S (EET? OR DHET? OR EPOXYEICOSATRIENO? OR DIHYDROXYEICOSATRIENO
L3            2 S L1 AND L2

     FILE 'STNGUIDE' ENTERED AT 15:58:00 ON 13 FEB 2003

     FILE 'CAPLUS' ENTERED AT 16:07:00 ON 13 FEB 2003

     FILE 'STNGUIDE' ENTERED AT 16:10:18 ON 13 FEB 2003

     FILE 'STNGUIDE' ENTERED AT 16:20:49 ON 13 FEB 2003

     FILE 'CAPLUS' ENTERED AT 16:28:18 ON 13 FEB 2003
L4        532334 S (HETE? OR EPOXYEICOSADIEN? OR EPOXYEICOSAMONO? OR EPOXYEICOSA
L5        532334 S (HETE? OR EPOXYEICOSADIEN? OR EPOXYEICOSAMONO? OR EPOXYEICOSA
L6           14 S L5 AND L1
L7         2806 S (HETE# OR EPOXYEICOSADIEN? OR EPOXYEICOSAMONO? OR EPOXYEICOSA

=> s l7 and l1
L8            1 L7 AND L1

=> d l8 abs ibib kwic 1

L8   ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2003 ACS
AB   The role of arachidonate lipoxygenase activity in reoxygenation
     induced cell injury in adult canine cardiac myocytes was
     investigated.  The prodn. of hydroxyeicosatetraenoic acids (HETEs
     ), which are lipoxygenase metabolites, was measured with high pressure
     liq. chromatog. in canine cardiac myocytes cultured under hypoxic
     conditions and then reoxygenated.  Free radical generation was
     evaluated by ESR spectroscopy with a spin trapper, 5,5-dimethyl-1-
     pyrroline N-oxide (DMPO) and luminol enhanced chemiluminescence emission.
     Cell injury was estd. in terms of morphol. changes and release of
     intracellular enzymes.  Morphol. damage to myocytes was quantified in
     terms of the percentage of hypercontracted "round" cells.  The effects of
     nordihydroguaiaretic acid, AA-861, mepacrine, indomethacin, aspirin,
     .alpha. tocopherol, and 2-0-octadecylascorbic acid (CV-3611) on
     lipoxygenase metab., free radical generation and cell injury
     were also assessed.  Cardiac myocytes produced 5-HETE and 12-
     HETE at less than 0.1 ng.cntdot.mg-1 protein under normoxic
     conditions.  Prodn. of HETE was greatly increased at five hours
     of reoxygenation after 45 min of hypoxia [5-
     HETE=12.0(SEM 0.5), 12-HETE=23.6(1.1) ng.cntdot.mg-1
     protein].  Both DMPO-OH adduct generation and chemiluminescence emission
     were considerably increased after one to three hours of
     reoxygenation, although they increased only slightly after 45 min
     of hypoxia.  After five hours of reoxygenation, long
     rod cells gradually became deformed; 92.0% of the cells were converted to
     hypercontracted "round" cells.  Cell injury and HETE
     prodn. were significantly suppressed by nordihydroguaiaretic acid (10
     .mu.M), AA-861 (2 .mu.M), and mepacrine (10 .mu.M).  Indomethacin (10
     .mu.M) and aspirin (50 .mu.M) enhanced cell injury and
```

HETE prodn. .alpha. Tocopherol and CV-3611 greatly suppressed **cell** injury and free radical generation, but not **HETE** prodn. The arachidonate lipoxygenase metabolic pathway may have an important role in **reoxygenation** induced myocardial **cell** injury in adult cardiac myocytes, possibly because of the generation of free radicals.

ACCESSION NUMBER: 1994:160464 CAPLUS
DOCUMENT NUMBER: 120:160464
TITLE: Free radical generation coupled with arachidonate lipoxygenase reaction relates to reoxygenation induced myocardial cell injury
AUTHOR(S): Kuzuya, Tsunehiko; Hoshida, Shiro; Kim, Youngjoon; Oe, Hiroshi; Hori, Masatsugu; Kamada, Takenobu; Tada, Michihiko
CORPORATE SOURCE: Sch. Med., Osaka Univ., Osaka, Japan
SOURCE: Cardiovascular Research (1993), 27(6), 1056-60
CODEN: CVREAU; ISSN: 0008-6363
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The role of arachidonate lipoxygenase activity in **reoxygenation** induced **cell** injury in adult canine cardiac myocytes was investigated. The prodn. of hydroxyeicosatetraenoic acids (**HETEs**), which are lipoxygenase metabolites, was measured with high pressure liq. chromatog. in canine cardiac myocytes cultured under **hypoxic** conditions and then **reoxygenated**. Free radical generation was evaluated by ESR spectroscopy with a spin trapper, 5,5-dimethyl-1-pyrroline N-oxide (DMPO) and luminol enhanced chemiluminescence emission. **Cell** injury was estd. in terms of morphol. changes and release of intracellular enzymes. Morphol. damage to myocytes was quantified in terms of the percentage of hypercontracted "round" cells. The effects of nordihydroguaiaretic acid, AA-861, mepacrine, indomethacin, aspirin, .alpha. tocopherol, and 2-0-octadecylascorbic acid (CV-3611) on lipoxygenase metab., free radical generation and **cell** injury were also assessed. Cardiac myocytes produced 5-**HETE** and 12-**HETE** at less than 0.1 ng.cntdot.mg-1 protein under normoxic conditions. Prodn. of **HETE** was greatly increased at five hours of **reoxygenation** after 45 min of **hypoxia** [5-**HETE**=12.0(SEM 0.5), 12-**HETE**=23.6(1.1) ng.cntdot.mg-1 protein]. Both DMPO-OH adduct generation and chemiluminescence emission were considerably increased after one to three hours of **reoxygenation**, although they increased only slightly after 45 min of **hypoxia**. After five hours of **reoxygenation**, long rod cells gradually became deformed; 92.0% of the cells were converted to hypercontracted "round" cells. **Cell** injury and **HETE** prodn. were significantly suppressed by nordihydroguaiaretic acid (10 .mu.M), AA-861 (2 .mu.M), and mepacrine (10 .mu.M). Indomethacin (10 .mu.M) and aspirin (50 .mu.M) enhanced **cell** injury and **HETE** prodn. .alpha. Tocopherol and CV-3611 greatly suppressed **cell** injury and free radical generation, but not **HETE** prodn. The arachidonate lipoxygenase metabolic pathway may have an important role in **reoxygenation** induced myocardial **cell** injury in adult cardiac myocytes, possibly because of the generation of free radicals.

=>

09/634,369

PATENT ASSIGNEE(S): The Brigham and Women's Hospital, Inc., USA; National Institutes of Health
SOURCE: PCT Int. Appl., 56 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001010438	A1	20010215	WO 2000-US21744	20000810
W: AU, CA, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 1207877	A1	20020529	EP 2000-952688	20000810
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY				

PRIORITY APPLN. INFO.: US 1999-148434P P 19990811
US 2000-634369 A2 20000809
WO 2000-US21744 W 20000810
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB **Epoxyeicosatrienoic** acids (**EETs**) are products of cytochrome P 450 epoxygenases that have vasodilatory properties similar to endothelium-derived hyperpolarizing factor (EDHF). The cytochrome P 450 isoform CYP2J2 was cloned and identified as a source of **EETs** in human endothelial cells. Physiol. concns. of **EETs** or overexpression of CYP2J2 decreased cytolcine-induced endothelial cell adhesion mol. expression and prevented subsequent leukocyte adhesion to the vascular wall by a mechanism involving inhibition of transcription factor NF-.kappa.B and I.kappa.B kinase (IKK). The inhibitory effects of **EETs** were independent of their membrane hypopolarizing effects suggesting that these mols. play an important non-vasodilatory role in vascular inflammation.

IT **Hypoxia**, animal
(prevention of **cell** death from **reoxygenation** following; anti-inflammatory actions of cytochrome P 450 epoxygenase-derived eicosanoids in combination with other agents)

IT 97717-69-6D, **Epoxyeicosatrienoic** acid, analogs
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); MFM (Metabolic formation); THU (Therapeutic use); BIOL (Biological study); FORM (Formation, nonpreparative); USES (Uses)
(anti-inflammatory actions of cytochrome P 450 epoxygenase-derived eicosanoids in combination with other agents)

IT 79551-81-8 79551-82-9 81246-84-6 81246-85-7 81276-02-0 81276-03-1 81920-20-9 81943-03-5 97717-69-6, **Epoxyeicosatrienoic** acid 218461-95-1, KMR-IV 87-27 325782-17-0, RKB-V 284-24
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anti-inflammatory actions of cytochrome P 450 epoxygenase-derived eicosanoids in combination with other agents)

=>

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=> s cell(p)hypoxi?(p)(re(w)oxygenat? or reoxygenat?)
       1618313 CELL
         34729 HYPOXI?
        110862 RE
         36976 OXYGENAT?
          2748 REOXYGENAT?
L1         638 CELL(P)HYPOXI?(P)(RE(W)OXYGENAT? OR REOXYGENAT?)

=> s (?EET? or ?DHET? or epoxyeicosatrieno? or dihydroxyeicosatrieno?)
'?EET?' NOT LONG ENOUGH FOR LEFT TRUNCATION
You have entered a truncated stem whose length is less than
the minimum allowed for left truncation in the requested
search field.  You may increase the length of the stem to
the minimum allowed and try again.  Enter HELP SFIELDS to
to find the minimum stem length for left truncation in
the requested search field.

=> s (?EET? or ?DHET? or epoxyeicosatrieno? or dihydroxyeicosatrieno? or
11,12(2a)EET or 11,12(2a)DHET or 14,15(2a)EET))
UNMATCHED RIGHT PARENTHESIS 'EET))'
The number of right parentheses in a query must be equal to the
number of left parentheses.

=> s (?EET? or ?DHET? or epoxyeicosatrieno? or dihydroxyeicosatrieno? or
11,12(2a)EET or 11,12(2a)DHET or 14,15(2a)EET)
'?EET?' NOT LONG ENOUGH FOR LEFT TRUNCATION
You have entered a truncated stem whose length is less than
the minimum allowed for left truncation in the requested
search field.  You may increase the length of the stem to
the minimum allowed and try again.  Enter HELP SFIELDS to
to find the minimum stem length for left truncation in
the requested search field.

=> s (EET? or DHET? or epoxyeicosatrieno? or dihydroxyeicosatrieno? or 11,12(2a)EET
or 11,12(2a)DHET or 14,15(2a)EET)
           813 EET?
           118 DHET?
           458 EPOXYEICOSATRIENO?
            93 DIHYDROXYEICOSATRIENO?
        779428 11
       1185077 12
         14300 11,12
                 (11(W)12)
           530 EET
            92 11,12(2A)EET
        779428 11
       1185077 12
         14300 11,12
                 (11(W)12)
            72 DHET
            12 11,12(2A)DHET
        720270 14
       1447939 15
          7534 14,15
                 (14(W)15)
           530 EET
```

epoxyeicosadien?

epoxyeicosamono?

epoxyeicosano?

HETE

```
           110 14,15(2A)EET
L2        1089 (EET? OR DHET? OR EPOXYEICOSATRIENO? OR DIHYDROXYEICOSATRIENO?
               OR 11,12(2A)EET OR 11,12(2A)DHET OR 14,15(2A)EET)

=> d his

     (FILE 'HOME' ENTERED AT 15:49:22 ON 13 FEB 2003)

     FILE 'CAPLUS' ENTERED AT 15:49:39 ON 13 FEB 2003
L1          638 S CELL(P)HYPOXI?(P)(RE(W)OXYGENAT? OR REOXYGENAT?)
L2         1089 S (EET? OR DHET? OR EPOXYEICOSATRIENO? OR DIHYDROXYEICOSATRIENO

=> s l1 and l2
L3            2 L1 AND L2

=> d l3 abs ibib kwic 1-2

L3   ANSWER 1 OF 2  CAPLUS  COPYRIGHT 2003 ACS
AB   CYP2J2 is abundant in human heart and its arachidonic acid metabolites,
     the epoxyeicosatrienoic acids (EETs), have potent
     vasodilatory, antiinflammatory and cardioprotective properties.  This
     study was designed to examine the role of CYP2J2 in hypoxia-
     reoxygenation-induced injury in cultured bovine aortic endothelial
     cells (BAECs).  Early passage BAECs were exposed to 24-h hypoxia
     followed by 4-h reoxygenation (HR).  HR resulted in cell
     injury, as indicated by significant increases in lactate dehydrogenase
     (LDH) release and trypan blue stained cells (p < 0.01) and was assocd.
     with a decrease in CYP2J2 protein expression.  Transfection of BAECs with
     the CYP2J2 cDNA resulted in increased CYP2J2 expression and arachidonic
     acid epoxygenase activity, compared with cells transfected with an
     irrelevant green fluorescent protein (GFP) cDNA.  HR induced significant
     injury in GFP-transfected BAECs, as indicated by increases in LDH release
     and trypan blue-stained cells (p < 0.01); however, the HR-induced injury
     was markedly attenuated in CYP2J2-transfected cells (p < 0.01).  HR
     increased cellular 8-iso-prostaglandin F2.alpha. (p < 0.05), and decreased
     eNOS expression, L-arginine uptake and conversion, and nitrite prodn. (p <
     0.01) in GFP-transfected BAECs.  CYP2J2 transfection attenuated the
     HR-induced increase in 8-iso-prostaglandin F2.alpha. (p < 0.05) and
     decreased the amt. of extracellular superoxide detected by cytochrome c
     redn. under normoxic conditions (p < 0.05) but did not significantly
     affect HR-induced decreases in eNOS expression, L-arginine uptake and
     conversion, and nitrite prodn.  Treatment of BAECs with synthetic
     EETs and/or epoxide hydrolase inhibitors also showed protective
     effects against HR injury (p < 0.05).  These observations suggest: (1) HR
     results in endothelial injury and decreased CYP2J2 expression; (2)
     transfection with the CYP2J2 cDNA protects against HR injury; and (3) the
     cytoprotective effects of CYP2J2 may be mediated, at least in part, by
     antioxidant effects.
ACCESSION NUMBER:         2001:552438  CAPLUS
DOCUMENT NUMBER:          135:240155
TITLE:                    Overexpression of cytochrome P450 CYP2J2 protects
                          against hypoxia-reoxygenation injury in cultured
                          bovine aortic endothelial cells
AUTHOR(S):                Yang, Baichun; Graham, Lerae; Dikalov, Serguei; Mason,
                          Ronald P.; Falck, John R.; Liao, James K.; Zeldin,
                          Darryl C.
CORPORATE SOURCE:         Division of Intramural Research, National Institute of
                          Environmental Health Sciences, National Institutes of
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Health, Research Triangle Park, NC, USA
SOURCE: Molecular Pharmacology (2001), 60(2), 310-320
CODEN: MOPMA3; ISSN: 0026-895X
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 70 THERE ARE 70 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB CYP2J2 is abundant in human heart and its arachidonic acid metabolites, the **epoxyeicosatrienoic** acids (**EETs**), have potent vasodilatory, antiinflammatory and cardioprotective properties. This study was designed to examine the role of CYP2J2 in **hypoxia-reoxygenation**-induced injury in cultured bovine aortic endothelial cells (BAECs). Early passage BAECs were exposed to 24-h **hypoxia** followed by 4-h **reoxygenation** (HR). HR resulted in **cell** injury, as indicated by significant increases in lactate dehydrogenase (LDH) release and trypan blue stained cells ($p < 0.01$) and was assocd. with a decrease in CYP2J2 protein expression. Transfection of BAECs with the CYP2J2 cDNA resulted in increased CYP2J2 expression and arachidonic acid epoxygenase activity, compared with cells transfected with an irrelevant green fluorescent protein (GFP) cDNA. HR induced significant injury in GFP-transfected BAECs, as indicated by increases in LDH release and trypan blue-stained cells ($p < 0.01$); however, the HR-induced injury was markedly attenuated in CYP2J2-transfected cells ($p < 0.01$). HR increased cellular 8-iso-prostaglandin F2.alpha. ($p < 0.05$), and decreased eNOS expression, L-arginine uptake and conversion, and nitrite prodn. ($p < 0.01$) in GFP-transfected BAECs. CYP2J2 transfection attenuated the HR-induced increase in 8-iso-prostaglandin F2.alpha. ($p < 0.05$) and decreased the amt. of extracellular superoxide detected by cytochrome c redn. under normoxic conditions ($p < 0.05$) but did not significantly affect HR-induced decreases in eNOS expression, L-arginine uptake and conversion, and nitrite prodn. Treatment of BAECs with synthetic **EETs** and/or epoxide hydrolase inhibitors also showed protective effects against HR injury ($p < 0.05$). These observations suggest: (1) HR results in endothelial injury and decreased CYP2J2 expression; (2) transfection with the CYP2J2 cDNA protects against HR injury; and (3) the cytoprotective effects of CYP2J2 may be mediated, at least in part, by antioxidant effects.

L3 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2003 ACS

AB **Epoxyeicosatrienoic** acids (**EETs**) are products of cytochrome P 450 epoxygenases that have vasodilatory properties similar to endothelium-derived hyperpolarizing factor (EDHF). The cytochrome P 450 isoform CYP2J2 was cloned and identified as a source of **EETs** in human endothelial cells. Physiol. concns. of **EETs** or overexpression of CYP2J2 decreased cytolcine-induced endothelial cell adhesion mol. expression and prevented subsequent leukocyte adhesion to the vascular wall by a mechanism involving inhibition of transcription factor NF-.kappa.B and I.kappa.B kinase (IKK). The inhibitory effects of **EETs** were independent of their membrane hypopolarizing effects suggesting that these mols. play an important non-vasodilatory role in vascular inflammation.

ACCESSION NUMBER: 2001:114981 CAPLUS
DOCUMENT NUMBER: 134:173027
TITLE: Anti-inflammatory actions of cytochrome P450 epoxygenase-derived eicosanoids
INVENTOR(S): Liao, James K.; Zeldin, Darryl